

F11
cont'd 113. (Amended) An isolated polynucleotide according to claim 112, wherein the sequence is selected from the group consisting of residues 1-91, 92-185, and 186-282 of SEQ ID NO:10.

F12 118. (Amended) An isolated polynucleotide comprising a sequence selected from the group consisting of nucleotides 7-36, 274-303 and 566-592 of SEQ ID NO:9; or the group consisting of a reverse complement of a sequence selected from nucleotides 244-273, 528-557, 800-826 of SEQ ID NO:9, wherein the polynucleotide provides a specific hybridization probe for human Robo-2 mRNA (RNA equivalent of SEQ ID NO:9).

REMARKS

Amendments

The substitute Sequence Listing is identical to that as filed except for the addition of SEQ ID NO:13, which is identical to the Sax-3 C. elegans Robo sequence of Table 1 of the Specification as filed.

In adherence with 37 CFR 1.821-1.825, this response is accompanied by a diskette containing SEQ ID NOS 01-13 in computer readable form and a paper copy of the sequence information. The computer readable Sequence Listing was prepared through the use of the software program "PatentIn" provided by the Patent and Trademark Office. The sequence information recorded in computer readable form is identical to that of the written sequence listing submitted herewith. This submission introduces no new matter.

Claims 68, 79, 88, 100 and 112 are amended to expressly require that the polypeptide elicit a corresponding Robo-specific antibody; e.g. p.4, lines 20-21; p.8, lines 27 - p.10, line 28; p.12, lines 24-25; p.13, lines 20-27; p.29, lines 16-17; etc.

Claims 75, 85, 96, 108 and 118 are amended to expressly require that the polynucleotide provides a specific hybridization probe for the corresponding Robo mRNA; e.g. p.14, line 30 - p.17, line 18; p.20, line 30 - p.21, line 6; p.29, lines 14-16; p.31, lines 30-31; p.34, line 22 - p.35, line 4; etc.

These amendments introduce no new matter.

Specification

Table 1 (p.4, line 24 - p.8, line 25), including the sequences disclosed therein, were included with the application as filed; hence, those sequences can not be new matter. "Residues 1-942" of SEQ ID NO:4 and "residues 1-284" of SEQ ID NO:10 are merely references to the corresponding residues of the sequences of the Sequence Listing, also included with the application as filed. As there are several discrepancies between the Sax-3 version of the *C. elegans robo* sequence of our Table 1 and the corresponding residues 1-937 of the *C. elegans robo* sequence of our Sequence Listing, we have provided a substitute Sequence Listing which provides an additional SEQ ID NO:13, which is identical to the Sax-3 *C. elegans* sequence of Table 1 as filed. All the sequences of the substitute sequences were present in the application as filed.

35USC101 - utility

The invention relates to diagnostic probes that specifically detect Robo proteins or transcripts. Robo proteins comprise a key component of the body's nerve cell guidance system. In particular, the inventors disclose that Robo functions as the critical gatekeeper controlling midline crossing of spinal axons (Specification, p.2, line 28 - p.3, line 2). These neural guidance molecules provide for proper enervation during development, but also prevent regeneration of proper nerve pathways following spinal injuries in adults. Hence, Robo polypeptides are important targets for therapeutic intervention (e.g. Specification, p.13, line 28 - p.14, line 20) and the ability to trace the presence of Robo in spinal tissue (e.g. p.29, lines 16-17; p.14, line 30 - p.17, line 18; p.20, line 30 - p.21, line 6; p.29, lines 14-16; p.31, lines 30-31; p.34, line 22 - p.35, line 4; etc.) is critical to developing therapy for spinal injuries.

The claims are limited to particularly useful diagnostic probes. The polynucleotides of claims 68, 79, 88, 100 and 112 (and their dependencies) encode polypeptides which elicit a corresponding Robo-specific antibody probe. As taught by our Specification (supra), these probes are useful to trace the presence of Robo expression in tissue. The polynucleotides of claims 75, 85, 96, 108 and 118 (and their dependencies) provide specific hybridization probes for the corresponding Robo-1 mRNA. As taught by our Specification (supra), these probes are

useful to trace the presence of Robo expression in tissue.

35USC112, first paragraph

Claims 68-119 are supported by a specific and substantial, credible asserted utility, supra, and hence, one skilled in the art would clearly know how to use the claimed invention. In fact, use of Robo-specific probes as claimed is expressly described, e.g. p.29, lines 14-16 and 16-17.

Claims 81, 100, 102-104, 113-114 are supported by a proper written description; in particular:

residues 1-942 of SEQ ID NO:4 were disclosed in Table 1 as filed;

residues 1-937 of SEQ ID NO:6 correspond to the Sax-3 residues of Table 1 as filed, but have been replaced with new SEQ ID NO:13 and claim 92 has been canceled;

residues 1081-1095¹ of SEQ ID NO:8, were mistyped from the "1181-1195" disclosed in the Specification as filed (p.27, line 24 of Substitute Specification) and have been corrected;

residues 68-259 of SEQ ID NO:8, were disclosed on p.4, line 19 of the Specification as filed;

residues 82-185 of SEQ ID NO:10 were mistyped from the "92-185" disclosed in the Specification as filed (p.27, line 29 of Substitute Specification) and have been corrected; and

residues 1-284 of SEQ ID NO:10 were disclosed in Table 1 of the Specification as filed.

35USC102(a)

Claims 88-90 are free of the cited art. The Sptrembl-11 seq. O01632 was made of record by the present Examiner in her Action mailed 1/21/00; on the accompanying PTO-892 she indicated for this sequence a date of 7/1/97, and the accompanying sequence printout indicated a record creation date of 7/1/97, and a last annotation update date of 11/1/98. In addition, someone from the PTO handwrote on the record printout next to the 7/1/98 creation date, "Public availability date".

As we have previously explained, O01632 is identical in sequence to EMBL/GenBank

¹ We presume the Examiner's reference to residues "1081-95" represents a typographical error.

amino acid entry 1825710, which was generated and submitted by the same authors, but was reportedly released earlier, on Apr 21, 1997. 1825710 (and O01632) appear to encode residues 424-1297 of our SEQ ID NO:6.

Also on Apr 21, 1997, Genbank reportedly released U88183 and 1825711. U88183 (which we made of record in our Response transmitted on 2/7/00) is the sequence of X chromosome cosmid ZK377 and its annotation includes predicted open reading frames, including 1825710 and 1825711. 1825711 appears to encode residues 1-423 of SEQ ID NO:6. Hence, the sequence of natural *C. elegans robo* (SEQ ID NO:6, also known as *sax-3*, see p.28, line 2 of our specification) comprises a recombination of 1825710 and 1825711. Note that the annotation reference to the Wilson (1994) reference describing a chromosome III cosmid is not for any X chromosome sequence, but merely for methods used to sequence large parts of *C. elegans* chromosomes.

To the extent that the sequences of the 1825710 and 1825711 predicted reading frames are citeable art under 35USC102(a), our Supplemental Declaration under 37CFR1.131 (made of record with our Response mailed Aug 31, 2000) demonstrates that Applicants had possession of the claimed subject matter prior to their publication. Specifically, the Declaration shows that the full-length sequence encoding *C. elegans robo* (SEQ ID NO:6) was determined by Applicants prior to the April 21, 1997 publication dates of 1825710 and 1825711.

The present Action alleges that the publication date of U88183 is 2/14/97, however no support or documentation of any kind is offered to support this rejection, which is hence not compliant with 35USC132(a). The closest date of record we are able to identify is a 2/13/97 "submission" date for "reference 3" cited in the U88183 report, however this is expressly not a publication date nor does the citation describe what was submitted to whom.

Claims 108-110 are free of the cited art. As noted in our Second Declaration under 37CFR1.131 (filed with our Response mailed 8/31/00) the Word document appended thereto describes a cDNA sequence including the 5' UTR of Human Robo1 (bases 1-509) and Human Robo1 coding sequence (bases 510-5366) encoding amino acids 1-1619 of Human Robo 1. Claims 108-100 are limited to polynucleotide sequences within this cDNA; hence, Applicants have documented possession of the invention as claimed prior to the purported publication date

of the GenBank Accession No. Z95705.

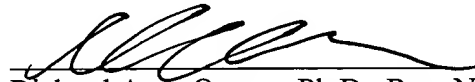
35USC103(a)

Claims 94-95 are free of the cited art because the GenBank Accession No. O01632 (U88183) upon which the Action principally relies is not prior art for the reasons explained above.

The Examiner is invited to call the undersigned if she would like to amend the claims to clarify the foregoing or seeks further clarification of the claim language.

Applicants hereby petition for any necessary extension of time pursuant to 37 CFR 1.136(a). The Commissioner is hereby authorized to charge any fees or credit any overcharges relating to this communication to our Deposit Account No. 19-0750 (order no. B98-006-2).

Respectfully submitted,
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VERSION MARKED TO SHOW AMENDMENTS

In the Specification

Last paragraph on p.4:

Table 1. Sequence Alignment of Robo Family Members: The complete amino acid alignment of the predicted Robo proteins encoded by *drosophila robo 1* (D1, SEQ ID NO:2) and Human *robo 1* (H1, SEQ ID NO:8) are shown. The extracellular domain of *C.elegans robo* (CE)[(SEQ ID NO:6, residues 1-937)] (SEQ ID NO:13); Sax-3; Zallen et al., 1997), the extracellular domain of *Drosophila robo 2* (D2)(SEQ ID NO:4, residues 1-942), and partial sequence of Human *robo 2* (H2)(SEQ ID NO:10, residues 1-284) are also aligned. The D2 sequence was predicted by the gene-finder program Grail. The position of immunoglobulin domains (Ig), fibronectin domains (FN), the transmembrane domain (TM), and conserved cytoplasmic motifs are indicated. The extracellular domain of rat *robo 1* is nearly identical to H1.

In the Claims

68. (Amended) An isolated polynucleotide comprising a coding strand encoding a polypeptide comprising a sequence of at least 12 consecutive residues of SEQ ID NO:2, wherein the polypeptide elicits a *Drosophila Robo-1* (SEQ ID NO:2) specific antibody.

75. (Amended) An isolated polynucleotide comprising at least 24 consecutive nucleotides of SEQ ID NO:1, wherein the polynucleotide provides a specific hybridization probe for *Drosophila Robo-1* mRNA (RNA equivalent of SEQ ID NO:1).

79. (Amended) An isolated polynucleotide comprising a coding strand encoding a polypeptide comprising a sequence of at least 12 consecutive residues of SEQ ID NO:4, wherein the polypeptide elicits a *Drosophila Robo-2* (SEQ ID NO:4) specific antibody.

85. (Amended) An isolated polynucleotide comprising at least 36 consecutive nucleotides of SEQ ID NO:3, wherein the polynucleotide provides a specific hybridization probe for *Drosophila Robo-2* mRNA (RNA equivalent of SEQ ID NO:3).

88. (Amended) An isolated polynucleotide comprising a coding strand encoding a polypeptide comprising a sequence of at least 12 consecutive residues of SEQ ID NO:6, wherein the polypeptide elicits a C. Elegans (SEQ ID NO:6) specific antibody.

96. An isolated polynucleotide comprising at least 24 consecutive nucleotides of SEQ ID NO:5, wherein the polynucleotide provides a specific hybridization probe for C. elegans Robo mRNA (RNA equivalent of SEQ ID NO:5).

100. (Amended) An isolated polynucleotide comprising a coding strand encoding a polypeptide comprising a sequence selected from the group consisting of residues 1-12, 18-28, 31-40, 45-65, 106-116, 137-145, 214-230, 274-286, 314-324, 399-412, 496-507, 548-565, 599-611, 660-671, 717-730, 780-791, 835-847, 877-891, 930-942, 981-998, 1040-1051, 1080-1090, 1154-1168, 1215-1231, and 1278-1302 of SEQ ID NO:8, or the group consisting of residues 6-21, 68-167, 168-258, 259-350, 351-450, 451-546, 547-644, 645-761, 762-862, 896-917, 1070-1079 and [1081-1095] 1181-1195 of SEQ ID NO:8, wherein the polypeptide elicits a human Robo-1 (SEQ ID NO:8) specific antibody.

102. (Amended) An isolated polynucleotide according to claim 100, wherein the sequence is selected from the group consisting of residues 6-21, 68-167, 168-258, 259-350, 351-450, 451-546, 547-644, 645-761, 762-862, 896-917, 1070-1079, and [1081-1095] 1181-1195 of SEQ ID NO:8. ?

108. (Amended) An isolated polynucleotide comprising a sequence selected from the group consisting of nucleotides 134-501, 502-776, 777-1049, 1051-1350, 1351-1636, 1637-1933, 1934-2284, 2285-2589, 2666-2765, 3169-3268, and 3514-3613 of SEQ ID NO:7; or the group consisting of nucleotides 199-228, 777-806, 1051-1080, 1352-1381, 1637-1666, 1934-1963, 2285-2313, 2643-2672, 3172-3200, and 3491-3520 of SEQ ID NO:7; or the group consisting of a reverse complement of a sequence selected from nucleotides 471-500, 751-777, 1021-1050, 1321-1350, 1607-1636, 1902-1931, 2257-2286, 2561-2591, 2761-2790, 3281-3310 and 3601-

3630 of SEQ ID NO:7, wherein the polynucleotide provides a specific hybridization probe for human Robo-1 mRNA (RNA equivalent of SEQ ID NO:7).

112. (Amended) An isolated polynucleotide comprising a coding strand encoding a polypeptide comprising a sequence selected from the group consisting of residues 5-16, 38-47, 83-94, 112-125, 168-180, 195-209, 222-235; and 241-254 of SEQ ID NO:10, wherein the polypeptide elicits a human Robo-2 (SEQ ID NO:10) specific antibody.

113. (Amended) An isolated polynucleotide according to claim 112, wherein the sequence is selected from the group consisting of residues 1-91, [82]92-185, and 186-282 of SEQ ID NO:10.

118. (Amended) An isolated polynucleotide comprising a sequence selected from the group consisting of nucleotides 7-36, 274-303 and 566-592 of SEQ ID NO:9; or the group consisting of a reverse complement of a sequence selected from nucleotides 244-273, 528-557, 800-826 of SEQ ID NO:9, wherein the polynucleotide provides a specific hybridization probe for human Robo-2 mRNA (RNA equivalent of SEQ ID NO:9).